UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/053,526	01/18/2002	Marie Dutreix	3754/OK213	1617

7590 09/24/2004

DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022

EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 09/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/053,526	DUTREIX ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-21 and 23-26* is/are rejected.

7)☒ Claim(s) *6 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/20/04* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1/23/04

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 20, 2004 has been entered.

Status

2. Claims 1-26 are pending.

Claims 1-21 and 23-26 are rejected.

Claim 22 is withdrawn from consideration.

Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Claim Rejections - 35 USC § 112

3. Claims 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 4, it is vague and indefinite how a "double stranded nucleic acid" can interact by Watson-Crick base pairing to the adaptor nucleic acid when the double stranded nucleic acid has no single stranded regions.

Response to Arguments – 112, second paragraph rejection

4. Applicant's arguments filed August 20, 2004 have been fully considered but they are not persuasive.

Applicant argues that claim 4 is definite because PNAs are capable of strand invasion and cites a post filing date reference which discusses the formation of D-loops by PNAs in double stranded DNA.

Applicant's argument does not make sense with regard to claim 4. Claim 4 is drawn to the donor nucleic acid, not to the single stranded "third strand oligonucleotide". The donor nucleic acid is the nucleic acid which undergoes "homologous recombination" according to the claim and which undergoes "Watson-Crick base pairing". Finally, claim 1 expressly recited the term "an adaptor segment comprising an oligonucleotide sequence". Claim 1 does NOT recited "an adaptor segment comprising a PNA sequence." If Applicant means to limit the claim to PNA adaptor nucleic acids, which are the only ones which can function to invade double stranded DNA, that limitation is not in the claims. Further, the cited portion of the specification, paragraph 0088, provides no teaching of "strand invasion" by a PNA. Finally, the specification itself provides no teaching whatsoever of the term "strand invasion" in a word search. Consequently, it remains unclear how nucleic acid adaptors composed of "oligonucleotides" and not "PNA"s can function in strand invasion as argued by Applicant.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 2, 4, 8-13, 15-21 and 23-26 are rejected under 35 U.S.C. 103(a) as being anticipated by Chan et al (J. Biol. Chem. (April 1999) 274:11541-11548) in view of Rubnitz et al (Mol. Cell. Biol. (1984) 4:2253-2258).

Chan teaches a method for effecting a homologous recombination between a native nucleic acid segment and a donor segment introduced into a cell (see abstract) comprising:

(a) introducing into a cell a nucleic acid targeting system (see page 11542, columns 1 and 2) comprising:

i) a third strand oligonucleotide which comprises a base sequence that forms a triple helix at a binding region on a native nucleic acid segment (see page 11543, figure 1, triplex forming domain and page 11542, column 1),

ii) an adaptor segment comprising an oligonucleotide able to bind at least a portion of the donor nucleic acid by Watson Crick base pairing which is linked to the third strand oligonucleotide (see page 11543, figure 1, where there is a oligonucleotide linked by a linker to the triplex forming domain. This linked oligonucleotide is deemed to be the adaptor segment for purposes of the rejection),

iii) a donor nucleic acid comprising a nucleic acid sequence homologous to the native nucleic acid segment so that the donor sequence is capable of undergoing homologous recombination with the native sequence at the target region (see page 11543, figure 1, where there is a single strand hybridized to the "donor" domain (here adaptor sequence) that is linked to the TFO oligonucleotide, and this single strand is capable of undergoing homologous recombination to repair the native sequence).

(b) allowing the third strand oligonucleotide to bind to the native nuclei acid segment to form a triple helix nucleic acid, thereby inducing homologous recombination at the native nucleic acid target region (see page 11543, figure 1, figure 2 and page 11542, subheading "In vitro triplex formation" and "intracellular targeting protocol"),

(c) allowing homologous recombination to occur between the native and donor nucleic acid segments (see page 11543, figure 1, figure 2 and page 11542, subheading "In vitro triplex formation" and "intracellular targeting protocol").

With regard to claim 2, Chan teaches preparation of the oligonucleotide by chemical synthesis (see page 11542, subheading "oligonucleotides").

With regard to claim 4, Chan teaches a double and single stranded donor nucleic acid (see page 11543, figure 1).

With regard to claim 8, 24 and 25, Chan teaches using a 30 nucleotide TFO region (see page 11543, AG30 domain used as TFO region).

With regard to claim 9, Chan teaches using an approximately 40mer nucleic acid as donor (see page 11543, figure 2).

With regard to claim 10, Chan teaches the use of an adaptor that is about 40 mer nucleic acid (see page 11543, figure 2).

With regard to claims 11-13, Chan teaches the use of a polyethyleneglycol linker (see 11544, figure 3 and page 11543, figure 2).

With regard to claims 15-21, Chan teaches correction of a mutation including base changes in an extrachromosomal, plasmid type, sequence (see page 11543, figure 2). Chan expressly recognizes the applicability to chromosomal correction (see page 11548, column 2).

With regard to claim 26, Chan teaches the addition of a 3' propylamine modification (see page 11542, column 1).

Chan does not teach the use of longer regions of homology, such as more than 100 to 1,000,000 bases as currently claimed.

Rubnitz teaches that longer the region of homology, the higher the level of homologous recombination (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Chan to use longer oligonucleotides, and in particular, longer than 214 nucleotides, since Rubnitz states "We have shown that the recombination frequency decreases as the homology is reduced, with the sharpest drop in recombination frequency occurring when the homology is reduced from 214 to 163 base pairs (see abstract)." An ordinary practitioner, reading Chan, would note that Chan was aware that short fragments were inefficient substrates for recombination (see page 11541, column 2) and Chan cited Rubnitz for this proposition. So an ordinary practitioner would wish to solve this problem, recognized by Chan, by applying the teaching of the cited reference, Rubnitz. Rubnitz shows in figure 3 that increasing length improves recombination efficiency and that 214 nucleotides in length is significantly better than 163 nucleotides in length, and that 5000 is better yet, therefore expressly suggesting that improved efficiency can be obtained by longer regions of homology. So the ordinary practitioner would follow Rubnitz teaching that 200 bp of homology is required for extrachromosomal recombination (see page 2257, column 1).

8. Claims 1-5, 8-13, 15-21 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al (J. Biol. Chem. (April 1999) 274:11541-11548) in view of Erdeniz et al (Genome Research (1997) 7:1774-1183).

Chan in view of Rubnitz teach the limitations of claims 1, 2, 4, 8-13, 15-21 and 23-26 as discussed above.

Chan in view of Rubnitz do not teach preparation of nucleic acid for recombination by PCR amplification.

Erdeniz teaches preparation of nucleic acid for recombination (see abstract) comprising the steps:

(a) providing a pair of primers complementary to a target native sequence (see page 1181, table 2),

(b) amplifying said first nucleic acid sequence (see page 1181, subheading "PCR"),

(c) isolating the amplification thus obtained (see page 1182, column 2),

(d) initating a recombination event (see page 1177, figure 3, for example).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to synthesize the nucleic acid constructs of Chan in view of Rubnitz by use of the PCR reaction as taught by Erdeniz since Erdeniz states "The advantages of these methods are that any mutation can be created easily using PCR primers without any need for cloning (see page 1174, column 2 to page 1175, column 1)." Erdeniz also recognizes that these approaches have some drawbacks, most notably low integration frequency (see page 1175, column 2)." Thus, an ordinary practitioner, who wished to take advantage of the ease of mutation generation by PCR but who wished to avoid the cost of low integration frequency would have been motivated to link the PCR generated fragment to a TFO oligonucleotide as taught by Chan since Chan expressly notes that use of the TFO domain increases recombination by up to 50 fold (see abstract).

9. Claims 1, 2, 4, 8-21 and 23-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al (J. Biol. Chem. (April 1999) 274:11541-11548) in view of Rubnitz and further in view of Sato et al (U.S. Patent 5,770,408).

Chan in view of Rubnitz teaches the limitations of claims 1, 2, 4, 8-13, 15-21 and 23-26 as discussed above. Chan in view of Rubnitz does not teach the use of a hexaethyleneglycol linker.

Sato teaches the use of a hexaethyleneglycol linker (see column 6, lines 19-21). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to synthesize the nucleic acid constructs of Chan in view of Rubnitz by use of the hexaethyleneglycol linker of Sato since Sato states that the hexaethyleneglycol linker is a desirable linker. Further, an ordinary practitioner would select this linker because it is nuclease resistant as well as being an equivalent linker to the linker used by Chan. MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." Here, the hexaethyleneglycol linker is a known equivalent to the linker of Chan.

Response to Arguments – 103 Rejection

10. Applicant's arguments filed August 20, 2004 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in each of the rejections as discussd above. Applicant's entire arguments with regard to motivation is that Applicant does not find the reasoning sufficient. That is not the standard. The standard is whether the ordinary practitioner would have found the invention prima facie obvious in view of the motivations presented. The motivations presented above are found sufficient to render the claimed invention prima facie obvious. No evidence of any secondary consideration is currently present.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does

not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claim Rejections - 35 USC § 112

11. The rejection of claims 1-21 and 23-26 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the new limitation to the claims requiring the method to be performed on "ex vivo" cells.

Allowable Subject Matter

12. Claims 6 and 7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

13. The following is a statement of reasons for the indication of allowable subject matter: Claim 6 and 7 are drawn to an embodiment in which one of the primers is removed from the construct after amplification by destruction of a ribonucleotide at the 3' end of the primer. While there is abundant prior art teaching PCR amplification with ribonucleotides at the 3' end, followed by removal of the PCR primer, there is no particular motivation found in these prior art references, such as Richards et al (U.S. Patent 5,876,976), to perform the method at only one primer site, since Richards is interested in reducing carryover, not in preparing a construct for nucleic acid targeting. Therefore, there is no teaching or suggestion of the limitations of claims 6 and 7 in the cited prior art.

Conclusion

14. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
2/5/09